UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

April 29, 2010

MEMORANDUM

SUBJECT: Oxamyl: benchmark dose analysis of cholinesterase data from a single 21-day dermal toxicity study in rabbits, and revision of the dermal point of departure for single chemical risk assessment.

PC Code: 103801
Decision No.: 432479
Petition No.: NA
Risk Assessment Type: NA
TXR No.: 0055350
MRID No.: NA

DP Barcode: D376936
Registration No.: RegRev-0253-1
Regulatory Action: NA
Case No.: NA
CAS No.: 23135-22-0
40 CFR: 180.3200

Ver.Apr.08

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MAY 4 RECD, 2010

I. CONCLUSIONS

This memo summarizes the results of a benchmark dose (BMD) analysis of cholinesterase (ChE) data from a single 21-day dermal toxicity rabbit study (MRID 40827601). This study was performed by DuPont in 1988. The newer 21-day dermal rabbit study (1999) has recently been re-evaluated (D373514) and is unacceptable (D376935, TXR 0055349) for use in risk assessment. This memo also summarizes the revision of the toxicological point of departure (PoD) based on the dermal BMD analysis.

II. BACKGROUND

On January 15, 2010, DuPont submitted a position paper for oxamyl detailing differences in the cholinesterase dose-response data from two 21-day dermal toxicity studies in rabbits (MRID 47958101). This submission suggested that a statistical evaluation of the ChE data from both studies should not be performed for BMD modeling. As part of the Agency review of this submission, HED considered the study protocols and ChE results from both studies (D373514, TXR 0055348). As a result of this review, the newer 21-day dermal study (MRID 44751201) was considered unacceptable/non-guideline due to critical flaws in the study (D376935, TXR 0055349). Therefore, the newer 21-day dermal study could not be used as part of BMD modeling for use in risk assessment. A new BMD analysis was performed based on the single acceptable/guideline 21-day dermal toxicity study in rabbits (MRID 40827601).

In the present analysis, BMD modeling has been used to estimate the dermal BMD_{10} and $BMDL_{10}$ for adult RBC and brain ChE data. The BMD_{10} is the estimated benchmark dose expected to result in 10% inhibition of ChE. The BMDL is the lower 95% confidence interval on the BMD_{10}. As a matter of science policy, EPA uses the BMDL for purposes of deriving points of departure in risk extrapolation (USEPA, 2000). The BMD_{10} was selected because it is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity and is a response level close to the background ChE. The exponential model utilized in the analyses of the oxamyl dermal data was based on the model that was used in the OP and NMC Cumulative Risk Assessments used in the OP and NMC Cumulative Risk Assessments (USEPA, 2001, 2002, 2005) to determine relative potency factors and points of departure. The exponential model and statistical methods used to calculate the BMD_{10}s and $BMDL_{10}$s have been supported by the FIFRA Science Advisory Panel (FIFRA SAP, 2001, 2002, 2005a, 2005b). Details of the "basic" exponential model used in this BMD analysis can be obtained at www.epa.gov/scipoly/sap/meetings/2001/september/rpfappendix1.pdf

III. RESULTS/DISCUSSION

Benchmark Dose Analysis

Detailed results of the BMD analysis (outputs) from MRID 40827601 are included in the Appendix. A summary of the BMD results is provided in the table below:

Table 1. BMD results from a 21-day dermal rabbit study (MRID 40827601)

Subset data	**BMD_{10}** mg/kg	**$BMDL_{10}$** mg/kg	**Model**
Brain	20.2071	15.8931	Exponential
RBC	23.0773	7.9949	Exponential

The results of the BMD analysis indicate that the brain and RBC BMD10s are similar. However, for single chemical risk assessment RBC cholinesterase inhibition is the most sensitive endpoint. The $BMDL_{10}$ for RBC cholinesterase inhibition is 7.9949 mg/kg.

Oxamyl Dermal and Inhalation Risk Assessment

The revised dermal BMD analysis results in a dermal point of departure of 8.0 mg/kg based on RBC ChE inhibition. Based on this revision, dermal risks may now be aggregated with inhalation risks (inhalation points of departure are 0.13 mg/kg for non-occupational and 0.39 mg/kg for occupational) since both endpoints are based on RBC ChE inhibition. However, the MOEs for the dermal and inhalation routes are not the same since the RfC methodology for inhalation results in an MOE of 30 and not 100 as is used for dermal. The Aggregate Risk Index (ARI) is the preferred aggregate approach when the uncertainty factors differ by routes of exposure (USEPA, 1998).

IV. REFERENCES

FIFRA Science Advisory Panel (SAP), 2001. "End Point Selection and Determination of Relative Potency in Cumulative Hazard Assessment: A Pilot Study of Organophosphorus Pesticide Chemicals."

FIFRA Science Advisory Panel (SAP), 2002. "Organophosphate Pesticides: Preliminary OP Cumulative Risk Assessment. Final Report."

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USEPA (1998). Memorandum from J.E. Whalan and H.M. Pettigrew to M. Stasikowski, Health Effects Division. "Inhalation Risk Characterizations and the Aggregate Risk Index (ARI)." Office of Pesticide Programs, Office of Prevention, Pesticides, and Toxic Substances, Washington, D.C.

USEPA, 2000. "Benchmark Dose Technical Guidance Document" Draft report. Risk Assessment Forum, Office of Research and Development, U.S. Environmental Protection Agency. Washington, DC. EPA/630/R-00/001

USEPA (2001). Preliminary Organophosphorus Pesticide Cumulative Risk Assessment. Office of Pesticide Programs, U.S. Environmental Protection Agency. Washington, DC. http://www.epa.gov/pesticides/cumulative/pra_op_methods.htm]

USEPA, 2002. Revised Organophosphorous Pesticide Cumulative Risk Assessment; June 10, 2002. Office of Pesticide Programs, U.S. Environmental Protection Agency. Washington, D.C. Available: http://www.epa.gov/pesticides/cumulative/rra-op/

USEPA 2005. Preliminary N-Methyl Carbamate Cumulative Risk Assessment. Office of Pesticide Programs, U.S. Environmental Protection Agency. Washington, DC. http://www.epa.gov/scipoly/sap/meetings/2005/index.htm#august]

APPENDIX

Oxamyl: adult male and female rabbit Brain
MRID NO: 40827601
EXPONENTIAL MODEL

***** UNWEIGHTED *****

BMD Grouped.

AIC: 94.56203

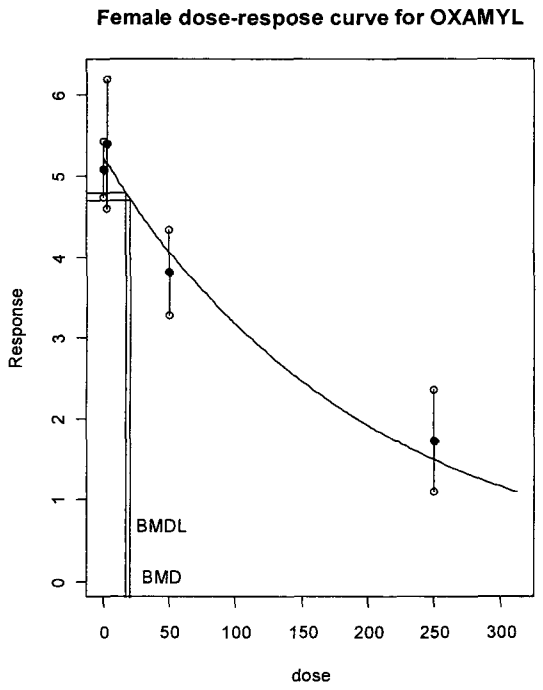
Female intercept estimate (standard error): 4.845178(0.2349891)
Male intercept estimate (standard error): 4.603611(0.2336164)
Grouped BMD10 estimate (standard error): 20.20715(3.378635)
The confidence intervals for the variables are given by

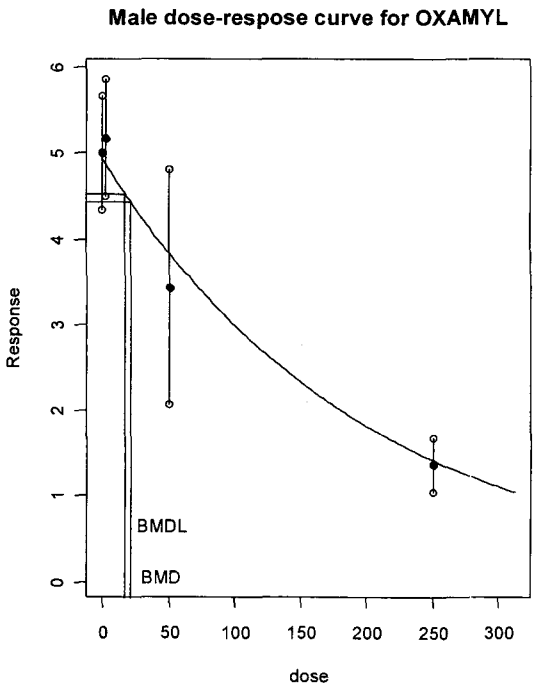
	lower	est.	upper
Female Intercept	4.416756	4.845178	5.315156
Male Intercept	4.179430	4.603611	5.070844
BMD10	15.143245	20.207147	26.964417

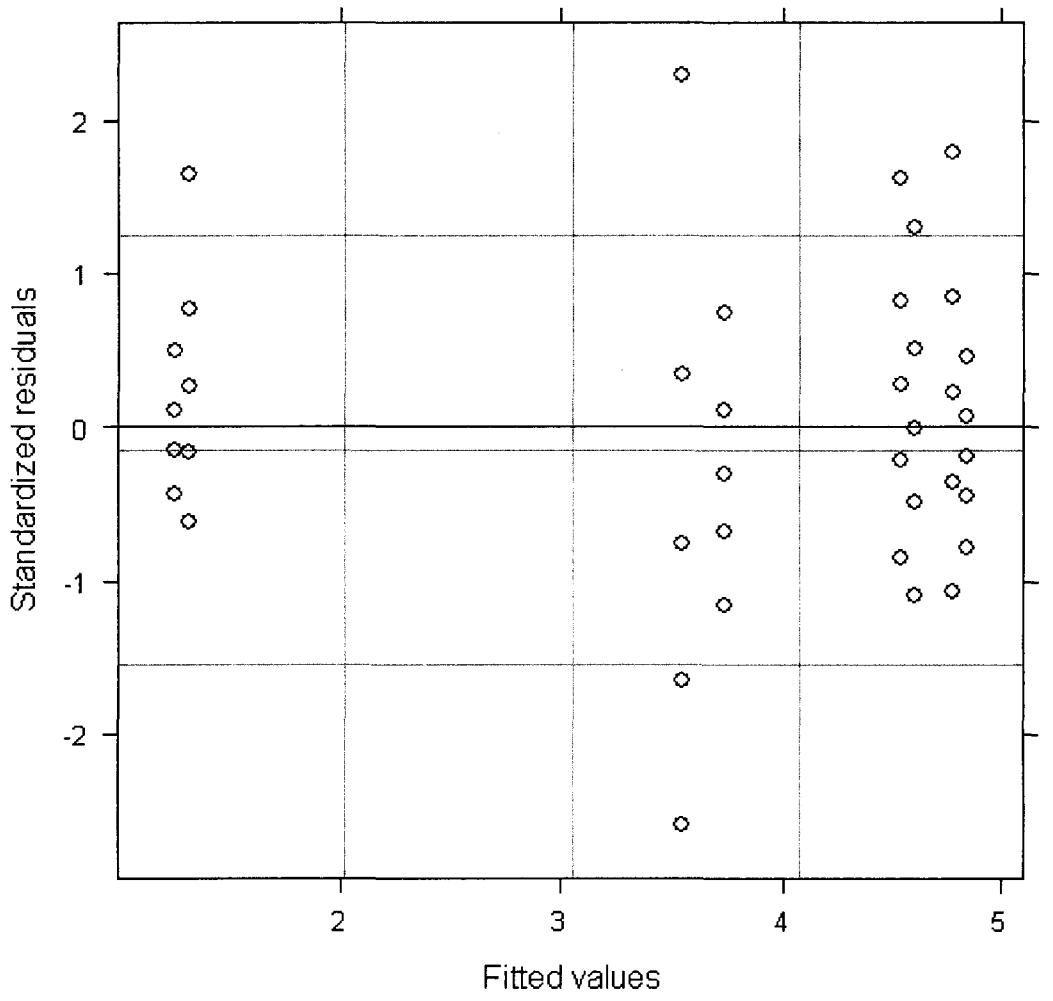
attr(,"label")
[1] "Coefficients:"

The one-sided confidence intervals (the lower bound) is given by

Female Intercept	Male Intercept	BMDL10
4.485799	4.247670	15.893149







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	1	2	3	4	5
CondIndex	8.285	2.806	1.786	1.562	1.000
mu	0.198	0.584	0.917	1.048	1.637
lA.sexF	0.202	0.114	0.306	0.372	0.008
lA.sexM	0.123	0.185	0.465	0.208	0.019
lD.(Intercept)	0.972	0.016	0.001	0.002	0.009
lD.sexM	0.020	0.894	0.004	0.037	0.044
lg	0.947	0.032	0.010	0.002	0.010

	lA.sexF	lA.sexM	lD.(Intercept)	lD.sexM	lg
lA.sexF	0.004	0.001	-0.020	0.006	-0.006
lA.sexM	0.001	0.005	-0.014	-0.007	-0.006
lD.(Intercept)	-0.020	-0.014	0.416	-0.060	0.160

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lD.sexM         0.006 -0.007        -0.060  0.141  0.001
lg             -0.006 -0.006         0.160  0.001  0.072
            lA.sexF lA.sexM lD.(Intercept) lD.sexM     lg
lA.sexF       1.000  0.123        -0.473  0.247 -0.354
lA.sexM       0.123  1.000        -0.320 -0.284 -0.347
lD.(Intercept) -0.473 -0.320         1.000 -0.247  0.922
lD.sexM       0.247 -0.284        -0.247  1.000  0.012
lg            -0.354 -0.347         0.922  0.012  1.000

----
Parameter Values and Relative Standard Errors (sigma == 1)
             Parms Relative SE
lA.sexF      1.568       0.066
lA.sexM      1.541       0.070
lD.(Intercept) 3.110     0.645
lD.sexM      -0.247      0.376
lg           -3.296      0.268

----
Mean Absolute Value of Gradient
                Val
lA.sexF      1.8990422
lA.sexM      1.7374864
lD.(Intercept) 0.6462198
lD.sexM      0.3019160
lg           1.2268468
```

Oxamyl: adult male and female rabbit RBC
MRID NO: 40827601
EXPONENTIAL MODEL

***** USING WEIGHTED *****

BMD Grouped.

AIC: 82.99818

Female intercept estimate (standard error): 4.790742(0.1355015)
Male intercept estimate (standard error): 4.850147(0.137352)
Grouped BMD10 estimate (standard error): 23.07731(29.54998)
Power parameter estimate (standard error): 0.5854223(0.1924199)

The confidence intervals for the variables are given by

	lower	est.	upper
Female Intercept	4.5342486	4.7907423	5.061745
Male Intercept	4.5901678	4.8501470	5.124851
BMD10	6.4806513	23.0773110	82.177278
Power Parameter	0.3532234	0.5854223	0.970262

attr(,"label")
[1] "Coefficients:"

The one-sided confidence intervals (the lower bound) is given by

Female Intercept	Male Intercept	BMDL10	Power Parameter
4.5756894	4.6321706	7.9949286	0.3839974

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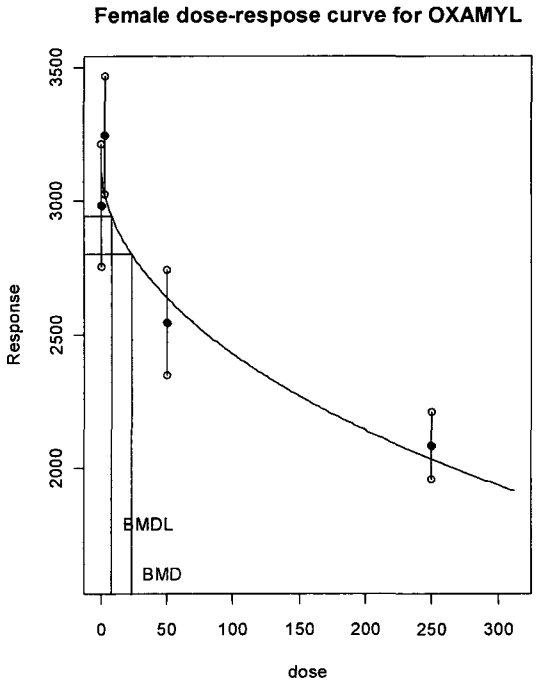
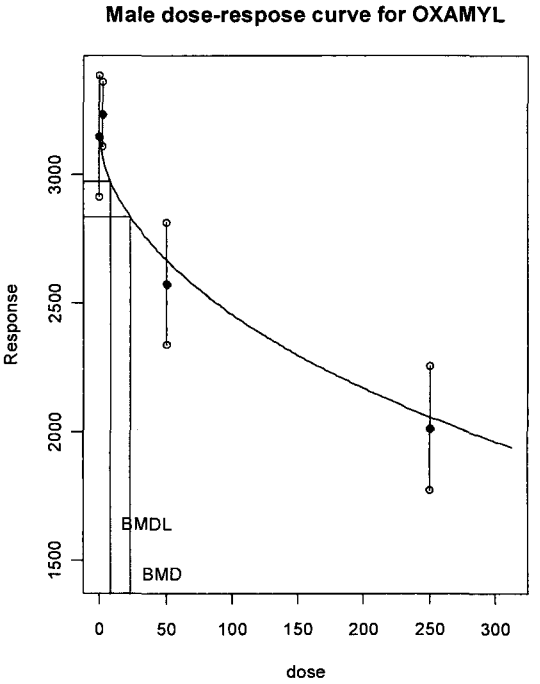
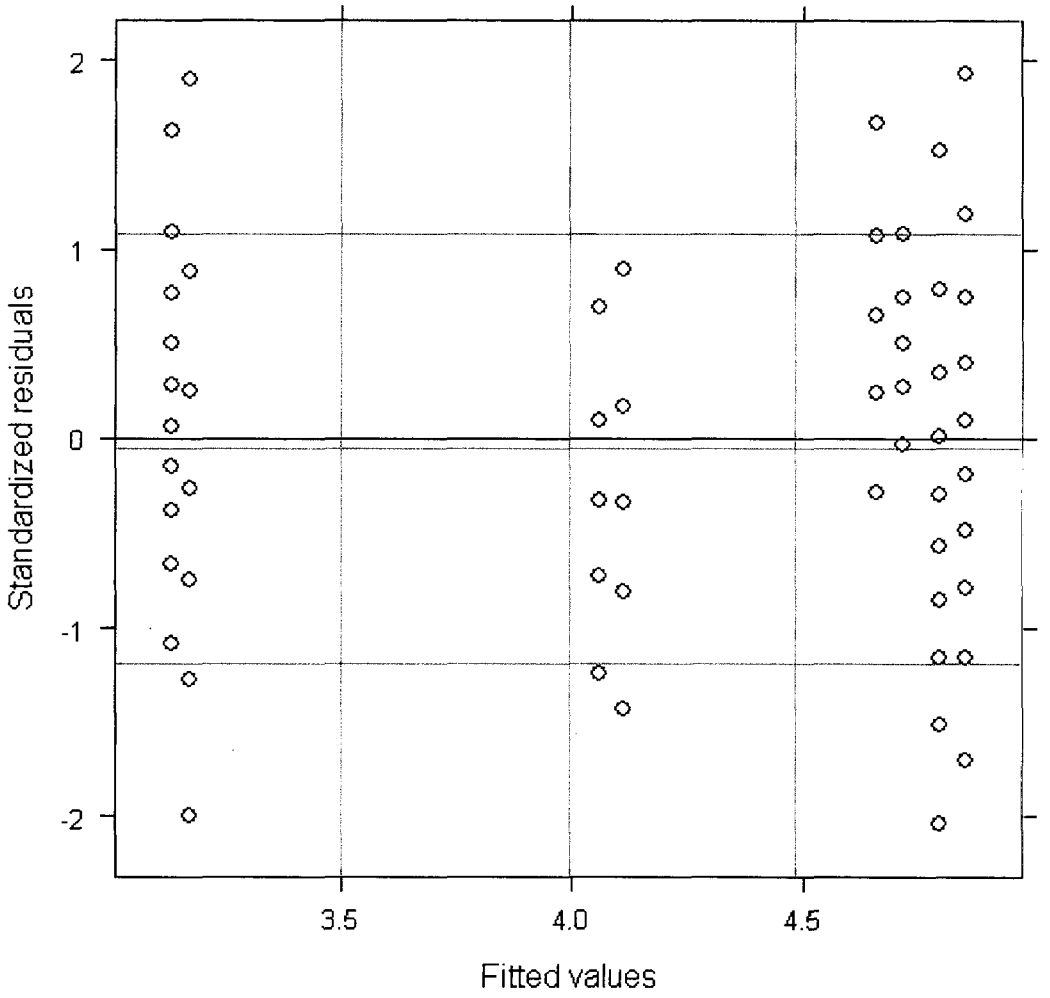

Female dose-respose curve for OXAMYL
Response
dose
BMDL
BMD
2000
2500
3000
3500
0
50
100
150
200
250
300


Male dose-respose curve for OXAMYL
Response
dose
BMDL
BMD
1500
2000
2500
3000
0
50
100
150
200
250
300



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	1	2	3	4	5
CondIndex	10.241	3.581	2.065	1.597	1.000
mu	0.167	0.477	0.827	1.069	1.708
lA.sexF	0.222	0.239	0.226	0.305	0.008
lA.sexM	0.161	0.172	0.511	0.134	0.022
lD.(Intercept)	0.970	0.022	0.002	0.001	0.005
lD.sexM	0.000	0.925	0.014	0.032	0.029
lg	0.950	0.033	0.010	0.001	0.006

	lA.sexF	lA.sexM	lD.(Intercept)	lD.sexM	lg
lA.sexF	0.003	0.000	-0.038	0.013	-0.010
lA.sexM	0.000	0.003	-0.026	-0.015	-0.012
lD.(Intercept)	-0.038	-0.026	1.530	-0.101	0.599
lD.sexM	0.013	-0.015	-0.101	0.456	0.059
lg	-0.010	-0.012	0.599	0.059	0.275

	lA.sexF	lA.sexM	lD.(Intercept)	lD.sexM	lg
lA.sexF	1.000	0.137	-0.529	0.325	-0.347
lA.sexM	0.137	1.000	-0.364	-0.397	-0.395
lD.(Intercept)	-0.529	-0.364	1.000	-0.121	0.922
lD.sexM	0.325	-0.397	-0.121	1.000	0.166
lg	-0.347	-0.395	0.922	0.166	1.000

Parameter Values and Relative Standard Errors (sigma == 1)

	Parms	Relative SE
lA.sexF	1.553	0.057
lA.sexM	1.591	0.057
lD.(Intercept)	3.361	1.237
lD.sexM	-0.297	0.675
lg	-0.495	0.525

Mean Absolute Value of Gradient

	Val
lA.sexF	2.1514667
lA.sexM	2.0171939
lD.(Intercept)	0.3264345
lD.sexM	0.1542710
lg	0.6363306

13544

R182095

Chemical Name: Oxamyl

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